The Role of the Immune System in the Pathogenesis of Psoriasis

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Psoriatic involved skin contains an increased number of activated T cells. The mechanism through which these T cells achieve and maintain their activated state is unknown, and both antigen-dependent and -independent mechanisms may contribute. Recently a novel pathway of antigen-independent T-cell activation has been described. This pathway is identified by a monoclonal antibody that binds to a T-cell membrane surface molecule termed "UM4D4." This molecule is expressed on a minority (20%) of psoriatic peripheral blood T cells but on a majority (75%) of the T cells in lesional skin. Thus, UM4D4 could play a role in antigen-independent T-cell activation in psoriasis. Indeed the monoclonal antibody anti-UM4D4 consistently induces proliferation of psoriatic UM4D4$^+$ T-cell clones. The activity of antigen-dependent pathways are also enhanced in psoriatic epidermis in as much as involved skin relative to uninvolved skin contains an increased number and function of antigen-presenting cells. Upon activation, the lesional T cells release lymphokines. Central to the immune hypothesis of psoriasis is that some of these T-cell lymphokines act on keratinocytes to induce changes characteristic of psoriasis. Indeed lymphokines from lesional psoriatic T-cell clones directly alter in vitro keratinocyte phenotype through induction of intercellular adhesion molecule-1 (ICAM-1) and HLA-DR cell-surface expression. Furthermore, the lymphokines also enhance keratinocyte growth. These data suggest a critical role for the immune system in the pathogenesis of psoriasis. *J Invest Dermatol 95:32S–34S, 1990*

Psoriasis is a multifactorial, genetic disease of controversial etiology that affects approximately 1–2% of the population in most countries. A dominant feature of the disease is that there is a significantly increased number of proliferating keratinocytes resulting in rapid epidermal turnover and the thickened, scaly, red plaques observed clinically. In addition, vascular expansion, fibroblast activation, and leukocytic infiltration are noted. However, it is not clear as to whether features of psoriasis such as increased vascularity, dermal and epidermal infiltration with leukocytes, and altered eicosanoid and cytokine profiles are a result of a primary defect in control of keratinocyte growth and/or cytokine release, or whether keratinocyte hyperproliferation occurs as a phenomenon secondary to cytokines released from activated cells in the dermis, such as those of the immune system.

Circumstantial evidence does indicate that the immune system plays an important role in the pathogenesis of psoriasis. As in other diseases with autoimmune features, psoriasis is associated with an increased frequency of certain HLA types, including HLA-B13, BW-17, BW-16, and BW-37 [1,2]. Furthermore, there is a strong correlation between HLA-B27 and HLA-BW38, and sacroilitis and distal arthritis in patients with psoriasis. In addition, the immunomodulatory effect of most anti-psoriatic agents points to the importance of the immune system in psoriasis. The dramatic and beneficial effect of cyclosporine A in the treatment of psoriasis provides strong evidence that the immune system plays a crucial role in the pathogenesis of this disease [3].

Cyclosporine A has inhibitory effects on epidermal antigen-presenting cell function, T-cell activation, and lymphokine release. Therapy with cyclosporine A for psoriasis results in clearing of immunocompetent cells from the skin before clinical effects are seen [4]. In contrast, cell-associated concentrations of cyclosporine A attainable in vivo do not appear to have any direct effects on growth of human keratinocytes [5]. The keratinocyte concentration of cyclosporine A necessary to inhibit keratinocyte proliferation in vitro is 20–50 times higher than the epidermal concentration obtained even after an in vivo dose of cyclosporine A as high as 14 mg/kg/d [5]. In contrast, this epidermal concentration attained in vivo is much higher than the lowest concentration necessary for inhibiting mitogen and antigen-induced T-cell activation. Cyclosporine A acts to inhibit expression of genes necessary for T-cell growth and function. Our attempts to detect similar inhibitory effects on genes involved in growth and function of cultured human keratinocytes including transforming growth factor-alpha, C-myc (J.T. Elder, personal communication) and epidermal transglutaminase activity, have been negative. Taken together, these data suggest that the in vivo effects of cyclosporine A on keratinocyte proliferation and differentiation in psoriasis are mediated through immune mechanisms. Other anti-psoriatic agents that are efficacious in treating psoriasis also suppress the immune system. Ultraviolet irradiation abrogates the function of Langerhans cells and induces the appearance of non-Langerhans-cell antigen-presenting cells that activate suppressor T-cell circuits. Topical corticosteroids deplete Langerhans cells of CD1 and HLA-DR molecules and abrogate epidermal antigen-presenting cell function. Corticosteroids also inhibit lymphokine release from T cells. The efficacy of methotrexate in rheumatoid arthritis as well as psoriasis may also be related to its ability to suppress cellular immune function. Retinoids, in addition to their effect on epidermal differentiation, alter antigen-presenting cell-T-cell interactions and depress human epidermal interleukin-1 production.

MECHANISMS OF T-CELL ACTIVATION IN PSORIASIS

As seen in other autoimmune diseases, such as rheumatoid arthritis, colitis, and diabetes mellitus, an early cellular event in the development of skin lesion in psoriasis is the infiltration of target tissue by

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macrophages and activated lymphocytes. We and others have found that even clinically uninvolved psoriatic skin contains an increased number of activated T cells. Elucidation of mechanisms through which psoriatic T cells achieve and maintain their activated state in lesions are critical for better understanding the pathogenesis of psoriasis.

T lymphocytes can be activated through multiple, distinct, but functionally related pathways. Such pathways can be both dependent and independent of antigens. Antigen-dependent T-cell activation occurs through interaction of the T-cell receptor CD3 complex with nominal antigenic peptides bound to major histocompatibility complex (MHC) proteins on antigen-presenting cells. Antigen-independent T-cell activation can occur through a variety of surface molecules, including CD2, CD28, and UM4D4. It is currently unknown whether T-cell activation in psoriasis occurs via foreign (i.e., microbial) antigen presentation by antigen-presenting cells, via activation of autoreactive T cells recognizing self-peptides on MHC molecules, or whether ligands are present in psoriatic skin that can directly activate T cells via antigen-independent activating surface molecules.

The CD1+DR+ Langerhans cells are the only bone marrow-derived antigen-presenting cells in normal human epidermis. However, we have shown that involved psoriatic skin, in contrast to normal skin, contains a high number of CD1−DR+ non-Langerhans antigen-presenting cells. Our functional studies demonstrated that these CD1−DR+ epidermal cells potently induced allogeneic T-cell activation and were responsible for the increased epidermal antigen presentation that we observed in involved psoriatic skin [6]. Thus, two conditions are present for activating T cells by antigen-dependent mechanisms in lesional psoriatic skin: elevated levels of the numbers and the function of antigen-presenting cells. To determine whether the elevated number of antigen-presenting cells was relevant for T cells actually present in psoriatic skin lesions, a T-cell line was initiated from an acute psoriatic skin lesion using recombinant human interleukin-2. Stimulation of the T-cell line with autologous involved psoriatic epidermal cells in the absence of added antigen resulted in profound proliferation and lymphokine release, including interleukin-2 and gamma-interferon [7].

However, as mentioned, antigen-independent pathways of T-cell activation may also contribute to chronic inflammation in a disease such as psoriasis. Recently a novel pathway of human T-lymphocyte activation identified by the monoclonal antibody, anti-UM4D4, has been described. Anti-UM4D4 identifies a surface structure termed UM4D4 and was generated against a synovial T-cell line from a patient with classical rheumatoid arthritis. The antibody reacts strongly with most rheumatoid synovial T cells and a small subset of peripheral blood T cells, resting or activated [8]. The monoclonal antibody anti-UM4D4 is mitogenic in soluble form for T-cell clones that express the molecule, even in the absence of accessory cells. Psoriasis and rheumatoid arthritis have some common features. Both are characterized by compartmentalization of activated T cells in association with hyperproliferation of local tissue (in psoriasis of the epidermis and in rheumatoid arthritis of the synovium). Furthermore, psoriatic patients have an increased incidence of arthritis. Because of these similarities, we asked whether UM4D4 expression was elevated on lesional psoriatic T cells, as it is on rheumatoid arthritis synovial T cells. Indeed, immunophenotyping of psoriatic skin biopsies showed that the majority of dermal and epidermal T cells expressed UM4D4. The mitogenic effects of anti-UM4D4 suggest that the surface structure, UM4D4, could play a role in the in vivo activation of a subset of T cells. Indeed, anti-UM4D4 consistently induced proliferation of T-cell clones obtained from involved psoriatic lesions [9]. The mechanism responsible for preferential recruitment of UM4D4+ T cells to the skin is unknown. UM4D4 may function like CD2 as both an activating molecule and a cell adhesion receptor, or cytokines released from keratinocytes may preferentially activate UM4D4+ T cells. Alternatively, T cells may activate UM4D4 as a consequence of residing in the milieu of the skin.

Thus several potential mechanisms of T-cell activation may be operative in psoriatic skin. Further studies are needed to dissect whether the increased antigen-presenting cell activity of lesional skin is occurring primarily via exogenous antigen, self-recognition, or through ligands that activate T cells through non-T-cell antigen-receptor pathways.

EFFECTS ON KERATINOCYTES OF LYMPHOKINES RELEASED FROM LESIONAL PSORIATIC T CELLS

Following activation, T cells release lymphokines that can act on other cells. Central to the immune hypothesis of psoriasis is that some of these T-cell lymphokines can act on keratinocytes to induce changes characteristic of psoriasis. We have demonstrated that lymphokines contained in conditioned medium from activated lesional psoriatic T-cell clones directly altered keratinocyte function through the induction of ICAM-1 and HLA-DR cell surface expression on cultured normal keratinocytes [9]. Thus, we have documented the existence of T cells in psoriatic skin that can directly induce keratinocytes to express the phenotype exhibited by psoriatic keratinocytes. This provides a critical link for the hypothesis that the expression of these molecules in lesional psoriatic epidermis is induced by activated local T cells.

The abnormal phenotype of psoriatic keratinocytes includes the expression of UM4D4 [10]. Basal keratinocytes adjacent to activated T cells demonstrated immunofluorescence localization of UM4D4 on their membrane in lesional psoriatic skin, but not in normal skin [10]. Thus UM4D4 expression is not limited to T cells and appears to function as a growth factor receptor on a UM4D4+ carcinoma cell line (unpublished data) as well as on T cells. Expression of UM4D4 on basal keratinocytes in rete pegs of psoriasis raises the very interesting possibility that the signals (lymphokines) that induce UM4D4 expression may make the keratinocyte more receptive to mitogenic growth factors or ligands that bind to UM4D4. However, although T cells may influence keratinocyte growth through induction of receptors (like UM4D4) that may increase their responsiveness to mitogenic signals, T cells may also stimulate keratinocyte proliferation both directly, via lymphokines, and indirectly, via induction of autocrine growth factors such as transforming growth factor alpha. Irrespective of the mechanism, various lesional psoriatic T-cell clones have clearly demonstrated the capacity in vitro to enhance keratinocyte proliferation [10]. Thus we have demonstrated that activated lesional psoriatic T cells do not only contain the capacity to induce keratinocyte expression of surface molecules seen in psoriasis but also contain the capacity to induce keratinocyte proliferation. This strongly suggests an important role for the immune system in the pathogenesis to psoriasis.

REFERENCES

1. White SH, Newcomer VD, Mickey MR, Terasaki PI: Disturbance of HL-A antigen frequency in psoriasis. N Engl J Med 287:740–743, 1972
2. Russell TJ, Schultes LM, Kuban D: Histocompatibility (HLA) antigens associated with psoriasis. N Engl J Med 287:738–740, 1972
3. Ellis CN, Gorsulowsky DC, Hamilton TA, Billings JK, Brown MD, Headington JT, Cooper KD, Baadsgaard O, Duell EA, Annesley TM, Turcotte JG, Voorhees JJ: Cyclosporine improves psoriasis in a double-blind study. JAMA 256:3110–3116, 1986
4. Gupta AK, Baadsgaard O, Ellis CN, Voorhees JJ, Cooper KD: Cyclosporine A therapy selectively reduces epidermal and dermal immune cells in psoriasis. Arch Dermatol Res 281:219–226, 1989
5. Fisher GJ, Duell EA, Nickoloff BJ, Annesley TM, Kowalke JK, Ellis CN, Voorhees JJ: Levels of cyclosporine in epidermis of treated psoriasis patients differentially inhibit growth of keratinocytes cultured in serum free versus serum containing media. J Invest Dermatol 91:142–146, 1988
6. Baadsgaard O, Gupta AK, Ellis CN, Voorhees JJ, Cooper KD: Psoriasis epidermal cells demonstrate increased numbers and function of non Langerhans cell antigen presenting cells. J Invest Dermatol 92:190–195, 1989
7. Baadsgaard O, Hansen E, Chan L, Tong P, Wantzin GL, Voorhees JJ,

Fox DA, Cooper KD: Lesional psoriasis T cell cultures reflect the in situ subset distribution and demonstrate autoreactivity. J Invest Dermatol 90:544, 1988

8. Higgs JB, Zeldes W, Kozarsky K, Schteingart M, Kan L, Bolke P, Krieger K, Davis W, Fox DA: A novel pathway of human T-lymphocyte activation. Identification by a monoclonal antibody generated against a rheumatoid synovial T cell line. J Immunol 140:3758, 1988
9. Baadsgaard O, Tong P, Elder JT, Hansen ER, Ho V, Hammerberg C, Vejlsgaard GL, Fox DA, Fischer G, Voorhees JJ, Cooper KD: UM4D4+ (CDw60) T-cells are compartmentalized into psoriatic skin and release lymphokines that induce a keratinocyte phenotype expressed in psoriatic lesions. J Invest Dermatol 95:275–287, 1990
10. Baadsgaard O, Fisher G, Fox DA, Salvo B, Carey T, Marcelo C, Voorhees JJ, Cooper KD: Conditioned media from lesional psoriatic T-cell clones induced keratinocyte proliferation and expression of the surface activation molecule UM4D4 (abstr). J Invest Dermatol 92:398A, 1989